Clinical trial results:
A Phase 3, 12-week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Evaulate the Efficacy of Oral Istradefylline 20 and 40 mg/day as Treatment for Subjects with Moderate to Severe Parkinson's Disease

Summary

EudraCT number	2013-002254-70
Trial protocol	DE IT CZ PL
Global end of trial date	12 October 2016

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	6002-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01968031
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kyowa Kirin Pharmaceutical Development, Inc.
Sponsor organisation address	212 Carnegie Center, Princeton, United States,
Public contact	Clinical Trial Help Desk, Kyowa Kirin Pharmaceutical Development, Inc., +1 888464-65747306, 6002014helpdesk@kyowakirin.com
Scientific contact	Clinical Trial Help Desk, Kyowa Kirin Pharmaceutical Development, Inc., +1 888464-65747306, 6002014helpdesk@kyowakirin.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2016
Global end of trial reached?	Yes
Global end of trial date	12 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the efficacy of istradefylline 20 and 40 mg/d for reducing the total hours of OFF time per day in moderate to severe PD patients with motor fluctuations and dyskinesia on levodopa combinations (levodopa/carbidopa and levodopa/benserazide) therapy.

Protection of trial subjects:

The Principal Investigators were responsible for the conduct and administration of the study in accordance with the protocol and ICH E6-GCP (CPMP/ICH/135/95) guidelines, for collecting, recording, and reporting the data accurately and properly as well as compliance with 21 CFR Parts 11, 50, 54, 56, and 312 and the applicable country-specific requirements and in accordance with the ethical principles enunciated in the Declaration of Helsinki adopted by the 18th World Medical Association (WMA) General Assembly in Helsinki, Finland (June 1964); and amended most recently in 2013 (ninth revision).
The Principal Investigator at each center was also responsible for contacts with study center management, the IEC/IRB, and with local non-regulatory bodies.
Agreement of the Investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the Sponsor and other forms as required by national authorities in the country where the study center was located.
The Investigator’s staff was responsible for preparing the study-specific written consent document for this study. The documents incorporated the required elements for informed consent, including the possible treatment risks and necessary documentation as required by the Declaration of Helsinki, 21 CFR Part 50, and the ICH-GCP (CPMP/ICH/135/95) guidelines. The ICF also was to contain any additional information required by local laws relating to IRB/IEC review. The ICF was approved by the IRB/IEC and the Sponsor.
The subject’s willingness to participate in the study was documented in writing (signed and dated by the subject [or by the subject’s legally acceptable representative] and by the person who conducted the informed consent discussion) with a copy provided to the subject. The
Investigators kept the original consent forms and copies were given to the subjects.

Background therapy:

Subjects were on levodopa plus a dopa decarboxylase inhibitor. Subjects were also on at least one additional approved dopaminergic treatment for PD, at recommended doses.

Evidence for comparator: -

Actual start date of recruitment	31 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Czech Republic: 68
Country: Number of subjects enrolled	Germany: 45

Country: Number of subjects enrolled	Italy: 59
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Israel: 35
Country: Number of subjects enrolled	Serbia: 25
Country: Number of subjects enrolled	United States: 278
Worldwide total number of subjects	613
EEA total number of subjects	242

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	313
From 65 to 84 years	297
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Recruitment opened in October 2013 and closed in July 2016.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects that met all inclusion/exclusion criteria as per protocol, were eligible for entry into the trial. A total of 828 subjects were screened of which 215 failed the screening process. 613 subjects were therefore enrolled into the trial.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were treated on an outpatient basis and instructed to take the assigned dose of study drug (placebo) in the morning with food; however, study drug was permitted to be taken without food if subjects did not routinely eat breakfast. There was no dose adjustment in this study.

Arm title	istradefylline 20 mg/d

Arm description: -

Arm type	Experimental
Investigational medicinal product name	istradefylline (KW-6002)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were treated on an outpatient basis and instructed to take the assigned dose of study drug (20 mg/d) in the morning with food; however, study drug was permitted to be taken without food if subjects did not routinely eat breakfast. There was no dose adjustment in this study.

Arm title	istradefylline 40 mg/d

Arm description: -

Arm type	Experimental

Investigational medicinal product name	istradefylline (KW-6002)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects were treated on an outpatient basis and instructed to take the assigned dose of study drug (40 mg/d) in the morning with food; however, study drug was permitted to be taken without food if subjects did not routinely eat breakfast. There was no dose adjustment in this study.

Number of subjects in period 1	Placebo	istradefylline 20 mg/d	istradefylline 40 mg/d
Started	204	202	207
Completed	186	182	178
Not completed	18	20	29
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	3	7	3
Failed inclusion criteria. Never received IMP	-	1	-
Adverse event, non-fatal	13	10	22
Not enough OFF time during baseline diary review	-	1	-
Protocol deviation	2	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	istradefylline 20 mg/d
Reporting group description: -	
Reporting group title	istradefylline 40 mg/d
Reporting group description: -	

Reporting group values	Placebo	istradefylline 20 mg/d	istradefylline 40 mg/d
Number of subjects	204	202	207
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	104	108	101
From 65-84 years	99	93	105
85 years and over	1	1	1
Age continuous Units: years			
arithmetic mean	63.8	63.6	64.5
full range (min-max)	41 to 86	41 to 87	40 to 85
Gender categorical Units: Subjects			
Female	80	77	81
Male	124	125	126

Reporting group values	Total		
Number of subjects	613		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	313		
From 65-84 years	297		
85 years and over	3		

Age continuous Units: years arithmetic mean full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	238		
Male	375		

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	istradefylline 20 mg/d
Reporting group description: -	
Reporting group title	istradefylline 40 mg/d
Reporting group description: -	

Primary: Change from baseline in the total hours of awake time per day spent in the OFF state	
End point title	Change from baseline in the total hours of awake time per day spent in the OFF state
End point description:	
End point type	Primary
End point timeframe:	
Total hours of awake time/day spent in the OFF state were measured at Baseline and Week 12 for the Primary Efficacy Endpoint	

End point values	Placebo	istradefylline 20 mg/d	istradefylline 40 mg/d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	198	194	200	
Units: Hours				
least squares mean (confidence interval 95%)	-0.88 (-1.19 to -0.58)	-1.2 (-1.52 to -0.89)	-1.15 (-1.46 to -0.84)	

Statistical analyses

Statistical analysis title	Primary Efficacy Endpoint Statistical Analysis
Comparison groups	Placebo v istradefylline 20 mg/d v istradefylline 40 mg/d
Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.17

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for any untoward medical occurrences from the time of signed Informed Consent through 30 days post dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	istradefylline 20 mg/d
Reporting group description: -	
Reporting group title	istradefylline 40 mg/d

Reporting group description: -

Serious adverse events	Placebo	istradefylline 20 mg/d	istradefylline 40 mg/d
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 204 (3.43%)	6 / 201 (2.99%)	8 / 207 (3.86%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical observation			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anaesthetic complication neurological			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mitral valve prolapse			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Parkinson's disease			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia, obstructive			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 204 (0.00%)	0 / 201 (0.00%)	1 / 207 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 201 (0.50%)	0 / 207 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	istradefylline 20 mg/d	istradefylline 40 mg/d
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 204 (54.41%)	117 / 201 (58.21%)	132 / 207 (63.77%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 204 (4.41%)	13 / 201 (6.47%)	18 / 207 (8.70%)
occurrences (all)	12	17	22
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	14 / 204 (6.86%)	23 / 201 (11.44%)	34 / 207 (16.43%)
occurrences (all)	14	30	37
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 204 (0.98%)	8 / 201 (3.98%)	12 / 207 (5.80%)
occurrences (all)	2	8	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2013	1) Subject Selection and the Inclusion Criteria were updated to remove all references to "intolerance" as related to levodopa or the class of antiparkinsonian medications. Inclusion criteria 5 and 7 have been combined to include subjects who are currently taking levodopa combinations (carbidopa/levodopa or benserazide/levodopa) with a total daily levodopa dosage of at least 400 mg plus a recommended, clinically effective dose of at least one adjunctive medication approved to treat Parkinson's disease such as a dopamine agonist, MAO-B inhibitor, or COMT inhibitor taken at the recommended dosages listed in the country-approved label for at least 2 weeks prior to randomization. (Note that subjects treated with anticholinergic medications or amantadine alone are not considered adequately treated with adjunctive antiparkinsonian medications and cannot be enrolled). 2) The Inclusion Criterion number 12 was updated to include subjects who are experiencing significant motor fluctuations while receiving levodopa plus adjunctive medication(s) as defined by an average of at least 2 hours OFF time on the three 24-hour ON/OFF patient diaries prior to the Baseline visit. 3) Flowchart of Study Procedures was updated to add footnote "f" to ensure that the inclusion criteria are reviewed to verify that subjects are experiencing significant motor fluctuations while receiving levodopa plus adjunctive medication(s) at Baseline. 4) The Baseline, Day 1 procedures were updated to specify that the three 24-hour patient diaries completed on 3 consecutive days immediately prior to the Baseline Day 1 visit will be reviewed to confirm that subjects are still experiencing significant motor fluctuations while receiving levodopa plus adjunctive medication(s). 5) Throughout the protocol, levodopa/carbidopa was updated to levodopa combinations (defined as levodopa/carbidopa or benserazide/levodopa).
29 July 2013	1) The Exclusion Criteria number 16 was updated to exclude subjects with mild, moderate, or severe hepatic impairment based upon Child-Pugh categorization of A, B, or C. Coagulation parameters were added to Table 9.3.2-1 Clinical Laboratory Assessments, and Appendix 9 was added with the Child-Pugh Categorization of the Severity of Liver Disease. 2) All references throughout the protocol to the QUIP scale have been updated to the QUIP-RS, including Appendix 12. 3) Text was added to Table 9.1-1 Study Schedule of Events, the PK Sampling Times Section, the Serious Adverse Events Section, and the Other Safety Considerations to instruct sites to attempt to collect a PK blood sample when SAEs occur. 4) Domperidone was indicated as an excluded medication in Section 8.1. In addition, Exclusion Criterion number 1 was updated to delete: (atypical dopamine antagonists [if approved in the country] are allowed).

26 September 2013	1) Adverse Event Contacts: Change in personnel noted. 2) Synopsis and protocol body: Correction of levodopa/carbidopa to levodopa combination (levodopa/carbidopa or benserazide/levodopa) therapy, as applicable. 3) Synopsis and Section 5.2: Update the approximate number of sites to 95. 4) Section 3.3 Nonclinical Overview: Wording was updated to clarify the nonclinical program results. 5) Section 7.5 and Table 9.1-1 Study Schedule of Events (footnote "d"): Clarification was made to add that the telephone contact will be made 30 days (± 7 days) "after the last dose of study drug" as follow-up for those subjects who discontinue prematurely from the study. 6) Section 9.2.2 Baseline Visit: Clarified wording to ensure that subjects will take the first dose of study drug at the Investigator's office and take the next dose of study drug the next morning (Day 2). In addition, the procedures done at the baseline visit were reordered to clarify how they are to occur. 7) Section 9.2.3 was updated to clarify that the three 24-hour patient diaries are to be completed on 3 consecutive days immediately prior to the scheduled visit. In addition, text was added to specify that the sites will instruct subjects not to take the study drug on the day of each clinic visit. 8) Section 9.3.2.3: was updated in the section describing orthostatic measurements to include heart rate (HR) where it was previously inadvertently omitted. 9) Other administrative, personnel changes, and correction of typographical and grammatical errors were made where needed.
15 August 2016	The purpose of this protocol amendment was to align the statistical wording with relevant changes as determined by amendments to the original Statistical Analysis Plan in follow-up to further dialogue with FDA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported